EXHIBIT I

REMAND EXHIBIT 3

EXHIBIT 9

The United States Experience With Oral Controlled-Release Morphine (MS Contin Tablets)

Parts I and II. Review of Nine Dose Titration Studies and Clinical Pharmacology of 15-mg, 30-mg, 60-mg, and 100-mg Tablet Strengths in Normal Subjects

ROBERT F. KAIKO, PhD,* ROBERT P. GRANDY, MS,* BENJAMIN OSHLACK, BPHARM,† JOSEPH FAV, PhD,† JOSEPH HORODNIAK, PhD,† GORDON THOMAS, BS,* ELLEN INGBER, MS,* AND PAUL D. GOLDENHEIM, MD*

The results of nine US multicenter, sequential crossover, dose titration studies of controlled-release oral morphine (MS Contin 30 mg tablets [MSC], Purdue Frederick, Norwalk, CT) are reviewed in Part I. The studies demonstrated the prolonged analgesic efficacy of the preparation in the treatment of patients with moderate to severe cancer-related pain. Approximately 93% of the patients achieved satisfactory to excellent analgesia on a 12-hour regimen when appropriate dose titration was allowed. The remaining patients were successfully maintained on an 8-hour regimen. The preparation was well-tolerated and comparable in safety to immediate-release oral morphine. In global evaluations, MSC was judged to be significantly ($P < 0.05$) more effective, and with significantly ($P < 0.05$) fewer side effects than both the prestudy opioid analgesics and 4-hour immediate-release oral morphine. Patients had a broad range of morphine requirements (mean daily MSC dose, 240 mg; range, 60 mg/day to 1800 mg/day); therefore various MSC tablet strengths were developed. Part II presents three studies in which the MSC formulations (15-mg, 60-mg, and 100-mg tablets) were compared to the 30-mg tablet within three randomized, single-dose, two-way crossover, analytically blinded bioavailability protocols, to determine bioequivalence and dose proportionality. The maximum morphine concentration, time of maximum morphine concentration, and area under the plasma morphine versus 12-hour and 24-hour time curve (AUC 0,12; AUC 0,24) were determined in each study. There were no significant differences between the values associated with MSC 1 × 30 mg tablet and 2 × 15 mg tablets (study 1), MSC 2 × 30 mg tablets and 1 × 60 mg tablet (study 2), and MSC 3 × 30 mg tablets and 1 × 100 mg tablet (study 3, values adjusted to dose of 90 mg), except for one marginally significant difference in study 3 (AUC 0,24; $P = 0.04$) which was not clinically or biopharmaceutically significant. The results showed that MSC 15-mg, 30-mg, 60-mg, and 100-mg dosage strengths are bioequivalent and dose proportional, and, therefore, therapeutically interchangeable. It was concluded that with routine assessment of the patient and adherence to the principles of analgesic dosing, MSC can be successfully used to control cancer-related pain. Furthermore, the availability of various MSC tablet strengths can be expected to facilitate the analgesic management of a patient population with widely differing opioid requirements.

Cancer 63:2348–2354, 1989.

THIS REPORT reviews the US dose titration studies on the oral controlled-release morphine preparation, MS Contin 30 mg tablets ([MSC] The Purdue Frederick Company, Norwalk, CT), and presents the results of studies that assessed the comparative bioavailability of various dosage strengths of the preparation. Individual dose titration studies have been discussed in detail elsewhere.[1–4] Part I of this article synthesizes these results and provides the background and rationale for the development of the dosage strengths described in Part II.

From the *Medical Department, The Purdue Frederick Company, Norwalk, Connecticut, and the †Purdue Frederick Research Center, Yonkers, New York.

Address for reprints: Robert F. Kaiko, PhD, Medical Department, The Purdue Frederick Company, 100 Connecticut Avenue, Norwalk, CT 06856.

Accepted for publication March 16, 1989.

Review of Dose Titration Studies

In randomized, double-blind, crossover comparative studies conducted in Canadian and European medical centers, MSC was administered every 12 hours to patients with cancer-related pain and found equally as effective as oral immediate-release morphine administered every 4 hours in equivalent daily doses.[5–13]

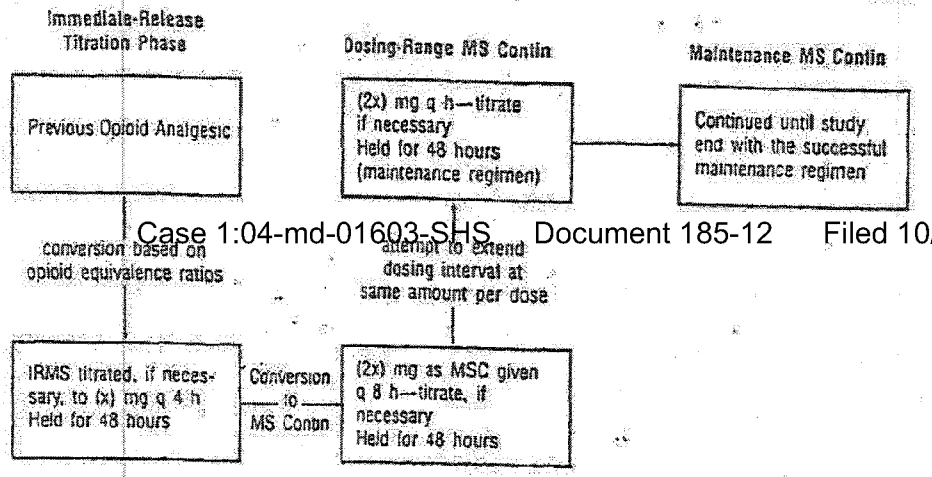

FIG. 1. Flow chart of study design for US dose titration studies.

In the US, nine dose titration studies assessed the comparative analgesic efficacy and safety of MSC 30 mg tablets, which led to the development of guidelines for use of the preparation in adult cancer patients with moderate to severe cancer-related pain.[1-8,14]

Patients and Methods

Each study was approved by an institutional review board and informed consent was obtained by all patients enrolled. Study participants consisted of adult cancer patients with moderate to severe cancer-related pain, no known hypersensitivity to morphine, and no evidence of major hepatic, renal, or cerebral dysfunction that could obscure evaluation of drug efficacy and safety.

The trials utilized a repeated-dose, sequential crossover, comparative study design, illustrated in Figure 1. Upon entering the study, virtually all patients received immediate-release oral morphine every 4 hours at doses equianalgesic to the prestudy drugs. Titration was usually required until the patients were stabilized. The patients were then converted to MSC, with the eventual goal being maintenance on a stable MSC dosage regimen that would provide acceptable pain relief without unacceptable side effects for at least 2 consecutive days. One set of protocols allowed dosage adjustment on the 12-hourly MSC schedule. The second set of protocols required that MSC be administered every 12 hours with no increase in the amount of morphine per dose (no titration allowed). Thus, in the second set of protocols, patients on the 12-hour MSC regimen received one third less daily morphine than on the 4-hourly and 8-hourly morphine schedules.

"Rescue" medication in the form of immediate-release morphine (*e.g.*, MSIR tablets, The Purdue Frederick Company Norwalk, CT) was available for breakthrough and incident pain and its use was documented. Comparative assessments of pain intensity, activity level, and side effects as well as global evaluations were carried out by patients and physicians.

Results

Of the 268 patients who entered the study, there were 50 discontinuations, of which ten were attributed to immediate-release oral morphine and two to MSC. The other discontinuations were not drug-related. The 218 patients who completed the study ranged in age from 18 to 84 (average age, 56 years old). The most common tumor sites were located in the lung (39 patients), breast (33), colon (19), prostate (17), cervix (14), and pancreas (ten).

The patients received a variety of prestudy opioid analgesics (including oxycodone combinations, hydromorphone, codeine combinations, methadone, and levorphanol). All 218 patients were successfully transferred to MSC from the prestudy analgesics and immediate-release morphine, and subsequently successfully maintained on an MSC regimen.

Under the protocols that allowed dosage adjustment on the 12-hour regimen, approximately 93% of the patients administered MSC every 12 hours achieved satis-

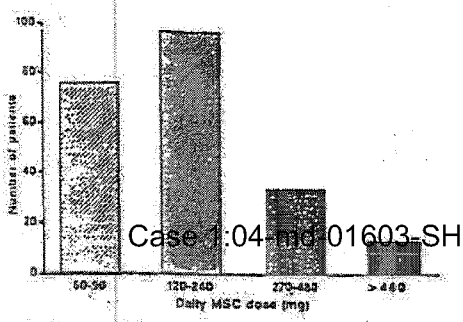

FIG. 2. Mean MS Contin daily dose administered to 218 cancer patients: data from nine US dose titration studies.

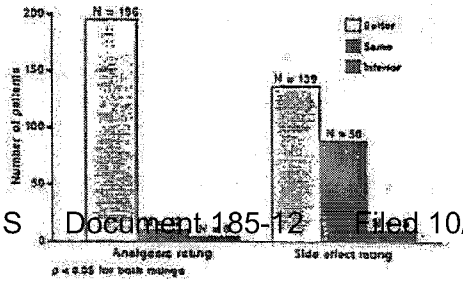

FIG. 3. Global evaluation of efficacy and side effects of MS Contin tablets versus prestudy analgesics.

factory to excellent analgesia. The remaining patients were successfully maintained on an 8-hour MSC schedule. Even in those studies in which the 12-hour regimen was associated with a one third dose reduction of daily morphine compared with the 4-hour and 8-hour morphine regimens, approximately 75% were successfully managed on the 12-hour MSC schedule. This finding supported both assay sensitivity (dose–response) and substantial success with the 12-hour MSC regimen, even at two thirds of the total daily morphine dosage of more frequent morphine schedules.

MSC was well-tolerated and comparable in safety to oral immediate-release morphine. There were no cases of respiratory depression. The side effects observed were those commonly associated with opioid analgesics, and included constipation, nausea, vomiting, and sedation. There was no evidence of drug accumulation with MSC.

Patients received a mean daily MSC dose of approximately 240 mg (range, 60–1800 mg/day) over an average of 16 days. Thus, patients required between two and 60 30-mg morphine tablets daily to control their pain. The majority of patients (67%) required a daily morphine dosage of 120 mg or more (Fig. 2). There was no significant difference in the total daily morphine dosage (mean ± SE) after administration of MSC (237 mg ± 19) *versus* immediate-release morphine (213 mg ± 15). The mean length of treatment with MSC was 16 ± 1.2 days *versus* an average of 4 ± 0.26 days with immediate-release morphine.

Global ratings showed MSC to be significantly ($P < 0.05$) more effective, and with significantly ($P < 0.05$) fewer side effects, than both the prestudy opioid analgesics and immediate-release morphine (Figs. 3 and 4).

Discussion

Results of these studies showed that with routine assessment of the patient and adherence to the principles of analgesic dosing, MSC can be successfully used to control cancer pain with a simplified oral regimen: every 12 hours for the vast majority of patients.

Overall, patients and investigators evaluated MSC to be greater than immediate-release morphine and the prestudy opioid analgesics in both effectiveness and safety ($P < 0.05$). These results differ somewhat from earlier double-blind European and Canadian studies in which immediate-release morphine and MSC were found to be equivalent in efficacy and side effects.[9–13] It is likely that the results in the nonblinded US studies were at least partially influenced by the patients' evaluation of the long and convenient duration of action with MSC, an assessment not possible in the double-blind studies in which patients received placebo every 4 hours along with MSC associated with every 12 hours. The value of the prolonged dosing interval MSC includes sustained pain relief, minimal intrusion into the patients' lives, improved compliance, and the opportunity for a full, uninterrupted night's sleep.

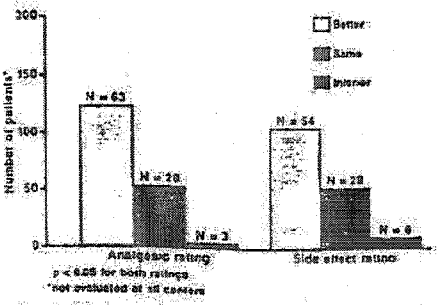

FIG. 4. Global evaluation of efficacy and side effects of MS Contin tablets versus immediate-release morphine.

Long-term poststudy follow-up data (up to 1 year for some patients) showed that tolerance was not a problem. Although mean morphine requirements increased slightly, approximately 50% of the patients had decreased or unchanged morphine requirements. Increased morphine requirements were almost always related to disease progression.

It was concluded that MSC is effective in providing prolonged analgesia for the management of patients with moderate to severe cancer-related pain, and is suitable in home as well as hospital settings.

Clinical Pharmacology of 15-mg, 30-mg, 60-mg, and 100-mg MS Contin Tablet Strengths in Normal Subjects

The results of these nine dose titration studies in cancer patients indicated the broad range of interindividual morphine requirements. It was apparent that alternate MSC tablet strengths were needed for opumal treatment of cancer pain. Various tablet strengths were formulated and comparative studies were designed to determine if the strengths were bioequivalent and dose proportional to the 30-mg MSC tablet. In addition to the 60-mg strength, which has recently become available in the United States, the 15-mg and 100-mg strengths were each separately studied in comparison to the 30-mg tablet. The three studies were conducted under similar protocols, described below.

Materials and Methods

Subjects: Each study involved between 20 and 24 healthy adult men who exhibited normal characteristics relative to age, build, and weight. The subjects had no history of drug abuse, had not received an opioid for at least 3 months before the studies, and were free of significant abnormal findings as determined by baseline physical examination, clinical laboratory tests, and vital signs. Subjects with a history of hypersensitivity to opioids were excluded from the studies. Each subject expressed his willingness to follow the protocol requirements through written, informed consent.

Test medications: In each study, the reference drug was 30-mg MSC tablets. Both reference and test medications were given in comparable doses. Thus, in study 1, two 15-mg MSC tablets were compared with one 30-mg tablet. In study 2, one 60-mg MSC tablet was compared with two 30-mg tablets. In study 3, one 100-mg MSC tablet was compared with three 30-mg tablets. No other drugs were used for at least 1 week before and during the studies.

Study design: The studies were conducted under randomized, single-dose, two-way crossover, nonblinded bioavailability protocols, with blinded analytical procedures.

After an overnight fast, 50% of the subjects received the reference medication and the remaining subjects received the test medication, according to a randomization code. The subjects remained upright and were not allowed food for another 4 hours. Blood samples for plasma morphine determination were obtained in a serial fashion immediately preceding drug administration (baseline) and at 14 intervals up to 24 hours after drug administration. After a 1-week washout period, the subjects were crossed over and received the alternative treatment. In both phases of the studies, the subjects remained within the testing facility during the 24-hour period after drug administration.

Plasma morphine analyses: Morphine analyses were conducted under blinded conditions using validated high performance liquid chromatography. This method is sensitive to 0.5 ng/ml (morphine base) and is highly specific. The technique does not cross-react with morphine-3-glucuronide, the major metabolite of morphine. The representative range of precision obtained from analysis of test samples was 2.2% to 5.9% and averaged 4.2%. Typical standard curves incorporated eight plasma morphine concentrations ranging from 1 to 70 ng/ml. Linearity was achieved through this range ($r = 0.999$).

Statistical analyses: The three pharmacokinetic values that determine bioequivalence were derived from the plasma morphine samples: maximum morphine concentration (C_{max}, ng/ml); time of maximum morphine concentration (T_{max}, hours); and area under the plasma morphine *versus* time curve (AUC, ng/ml × hour), calculated by the trapezoidal rule over 0 to 12 and 0 to 24 hour intervals.

Separate analyses of variance (ANOVAs) were calculated for the values. Statistical power calculations were carried out to validate the probability of the studies to detect differences between the treatment groups, if they truly existed. In addition, the Pitmaa-Morgan test for differences in variation was applied to the pharmacokinetic values to determine if the test formulations were intrinsically more variable than the reference medication.

Results

Figures 5 through 7 show the mean plasma morphine *versus* time curves for the subjects receiving single MSC doses of 2 × 15 mg *versus* 1 × 30 mg, 2 × 30 mg *versus* 1 × 60 mg, and 3 × 30 mg *versus* 1 × 100 mg. In each study, the curves were virtually superimposable.

The derived comparative mean pharmacokinetic values are graphically illustrated in Figure 8 and summarized in Table 1. There were no significant differences ($P \geq 0.05$) among values associated with the four MSC tablet strengths, except for one marginally significant value (AUC 0.24 in study 3; $P = 0.04$). The statistically observed

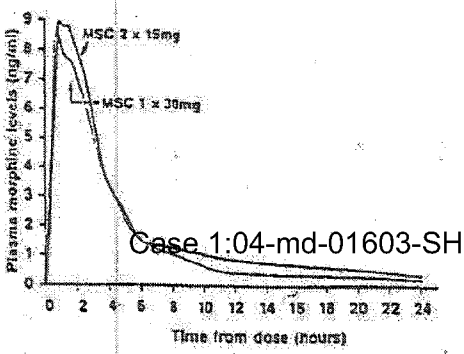

FIG. 5. Mean plasma morphine concentrations in normal subjects after single doses of one 30-mg MS Contin tablet and two 15-mg MS Contin tablets.

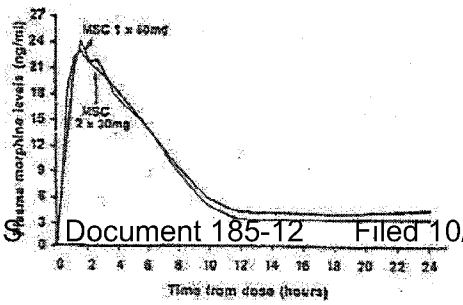

FIG. 6. Mean plasma morphine concentrations in normal subjects after single doses of two 30-mg MS Contin tablets and one 60-mg MS Contin tablet.

6% difference is not clinically significant. Nor is it important from a biopharmaceutical perspective in which a 20% difference is considered significant. Moreover, the AUC values associated with the 100-mg MSC tablet were adjusted to a total dose of 90 mg for comparison with the reference drug (3 × 30 mg MSC tablets). A more clinically useful comparison involves the unadjusted values, since one 100-mg tablet would be used in place of three 30-mg tablets. Without adjustment, all pharmacokinetic values associated with the 100-mg tablet were equal to those associated with the reference formulation. Thus, the 15-mg, 30-mg, 60-mg, and 100-mg MSC tablets were found to be bioequivalent and dose proportional.

The statistical power to detect a 20% difference between the treatment means was high for AUC and C_{max} comparisons; predictably, the T_{max} values were associated with a lower degree of power (Table 1). It should be noted that at the September 29 through October 1, 1986 meeting of the Bioequivalence Task Force of the Food and Drug Administration, Dr. S. Bolton presented empirical and theoretical evidence showing that T_{max} values are associated with a lower degree of power than are AUC and C_{max} values in comparative pharmacokinetic studies.

Tests for differences in variation revealed no significant differences among the tablet strengths.

Discussion

The results of these single-dose, two-way crossover studies demonstrate the pharmacokinetic bioequivalence and dose proportionality of MSC 15-mg, 30-mg, 60-mg, and 100-mg tablets, thus indicating therapeutic interchangeability among the dosage strengths.

This therapeutic interchangeability was confirmed in a randomized, double-blind comparative clinical study in which 51 cancer patients received either one 100-mg MSC tablet or three 30-mg MSC tablets every 12 hours.[15] Both tablet strengths provided equivalent analgesia and caused equally few side effects when administered in approximately equal morphine doses. These clinical data signify that the 100-mg MSC tablet can be substituted for three 30-mg MSC tablets without an increase in side effects or decrease in analgesic effectiveness.

It must be noted that the purpose of the single-dose pharmacokinetic studies was to compare the pharmacokinetic parameters of various MSC tablet strengths, but not to extrapolate pharmacokinetic data derived from young healthy volunteers to patients. The literature shows that factors such as age and both hepatic and renal function affect the pharmacokinetic characteristics of morphine.[16–20] Thus, pharmacokinetic data obtained in young normal volunteers do not duplicate those derived from patients.

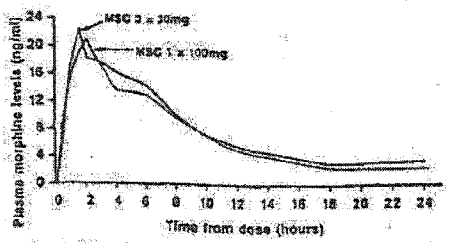

FIG. 7. Mean plasma morphine concentrations in normal subjects after single doses of three 30-mg MS Contin tablets and one 100-mg MS Contin tablet. Dose adjusted to 90 mg.

TABLE 1. Pharmacokinetic Values (Mean ± SE) Associated With Single Doses of MS Contin 30 mg Tablets (Reference Drug) *Versus* MS Contin 15, 60, and 100 mg Tablets

	Reference	Test agent	*P* (significance)	Power 1-beta
Study 1*				
AUC (0, 24) (ng/ml × hr)	55.8 ± 3	57.5 ± 3	0.5 (NS)	0.61
C_{max} (ng/ml)	10.0 ± 0.4	10.8 ± 0.4	0.2 (NS)	0.87
T_{max} (hr)	2.1 ± 0.1	1.8 ± 0.1	0.1 (NS)	0.57
Study 2†				
AUC (0, 24) (ng/ml × hr)	140.3 ± 6	135.4 ± 6	0.5 (NS)	0.89
C_{max} (ng/ml)	20.2 ± 0.8	20.2 ± 0.8	0.5 (NS)	0.93
T_{max} (hr)	2.3 ± 0.2	2.5 ± 0.2	0.5 (NS)	0.27
Study 3‡				
AUC (0, 24) (ng/ml × hr)	348 ± 10	369.6 ± 10	0.1 (NS)	0.64
C_{max} (ng/ml)	24 ± 2	23.2 ± 2	0.5 (NS)	0.46
T_{max} (hr)	2.2 ± 0.3	1.9 ± 0.1	0.2 (NS)	0.26

AUC: area under the plasma morphine *versus* time curve; C_{max}: maximum morphine concentration; T_{max}: time of maximum morphine concentration.

* Reference: 1 × 30 mg; test agent: 2 × 15 mg.

† Reference: 2 × 30 mg; test agent: 1 × 60 mg.

‡ Reference: 3 × 30 mg; test agent: 1 × 100 mg.

§ Value adjusted to total dose of 90 mg.

of the pain, recognition of the broad range of opioid requirements, administration of the appropriate dose of the appropriate drug in the most convenient regimen, prevention, and/or treatment of side effects (*e.g.*, constipation), and constant reassessment followed by proper titration.

REFERENCES

1. Homesley HD, Wetlander CE, Muss HB, Richards F. Dosage range study of morphine sulfate controlled-release. *Am J Clin Oncol* 1986; 9: 449–453.
2. Mood SD, Kleinman PM, Kantor TG, Blum RH, Savarese JJ. Management of cancer pain with oral controlled-release morphine sulfate. *J Clin Pharmacol* 1987; 27:155–161.
3. Khojasteh A, Evans W, Reynolds RD, Thomas G, Savarese JJ. Controlled-release oral morphine sulfate in the treatment of cancer pain with pharmacokinetic correlation. *J Clin Oncol* 1987; 5:956–961.
4. Savarese JJ, Shepherd L, Krant MJ. Long-acting oral morphine in cancer pain analgesia. *Clin J Pain* 1987; 3:177–181.
5. Brooks L, DeJager R, Blumenreich M, George E, Savarese JJ. Principles of cancer pain management: Use of long-acting oral morphine. *J Family Pract* 1989; 28:275–280.
6. Breasa FJ, Walsh M, Savarese JJ, Kaiko RF. A study of controlled-release oral morphine (MS Contin) in an advanced cancer hospital. *J Pain Symp Manag* 1987; 2:193–198.
7. Lapin J, Kaiko RF, Rogers AG *et al.* Cancer pain management with a controlled-release oral morphine preparation (Abstr). Presented at the Fifth Annual Meeting of the American Pain Society 1985; CP37.
8. Gucalp E, Balkin W, DeFalco K *et al.* The use of controlled release oral morphine in terminal cancer patients (Abstr). Proceedings of the International Conference on Supportive Care in Oncology, Brussels, Belgium. 1988; 146.
9. Hanks GW, Trueman T. Controlled-release morphine tablets are effective in twice-daily dosage in chronic cancer pain. In: Wilkes E, Levy J, eds. Advances in Morphine Therapy: International Congress and Symposium Series, no. 64. London: The Royal Society of Medicine, 1984; 103–105.
10. Walsh TD. A controlled study of MST Continus tablets for chronic pain in advanced cancer. In: Wilkes E, Levy J, eds. Advances in Morphine Therapy: International Congress and Symposium Series, no. 64. London: The Royal Society of Medicine, 1984; 99–102.
11. Henriksen H, Knudsen J. Controlled evaluation and ongoing experience with sustained release morphine in patients with advanced cancer pain. In: Band PR, Stewart JH, Towsen RT, eds. Advances in the Management of Chronic Pain: The International Symposium on Pain Control: Toronto, Canada. Toronto: Purdue Frederick, 1986: 69–72.
12. Arkinstall W, Goushaour B, Stewart J, White J. Double-blind crossover comparison between sustained release morphine tablets and oral morphine solution in patients with severe pain: A preliminary report. In: Band PR, Stewart JH, Towsen RT, eds. Advances in the Management of Chronic Pain: The International Symposium on Pain Control: Toronto, Canada, Toronto: Purdue Frederick, 1986; 51–56.
13. Welsh J, Stuart JFB, Hayeshaw T, Billiaert P, Calman KC. A double blind cross-over study of two oral formulations of morphine. In: Harrap KR, Davis W, Calvert AH, eds. Cancer Chemotherapy and Selective Drug Development. Proceedings of the 10th Anniversary Meeting of the Coordinating Committee for Human Tumor Investigations, Brighton, England. Boston: Martinus Nijhoff, 1984: 153–158.
14. The Purdue Frederick Company. Clinical reports on file. Norwalk, CT.
15. Ponesny RK, Maldonado M, Fitzmarun R, Kaiko RF, Kanner R. Controlled-release morphine sulfate: Analgesic efficacy and side effects of a 100 mg tablet in cancer pain patients. *Cancer* 1989; 63:2284–2288.
16. Kaiko RF, Wallenstein SL, Rogers AG, Grabinski PY, Houde RW. Narcotics in the elderly. *Med Clin North Am* 1982; 66:1079–1089.
17. Owen JA, Sitar DS, Berger L, Brownell L, Duke PC, Mitenko PA. Age-related morphine kinetics. *Clin Pharmacol Ther* 1983; 34:364–368.
18. Sawe J. High dose morphine and methadone in cancer patients: Clinical pharmacokinetic considerations of oral treatment. *Clin Pharmacokinet* 1986; 11:87–106.
19. Moore A, Sear J, Baldwin D *et al.* Morphine kinetics during and after renal transplantation. *Clin Pharmacol Ther* 1984; 35:641–645.
20. Ball M, McQuay HJ, Moore RA, Allen MC, Fisher A, Sear J. Renal failure and the use of morphine in intensive care. *Lancet* 1985; 1:784–786.
21. Thirlwell MP, Mount BM, Maroun JA *et al.* Pharmacokinetics of oral morphine solution and controlled-release morphine tablets in cancer patients. *Cancer* 1989; 63:2275–2283.
22. Savarese JJ, Goldenheim PD, Thomas GB, Kaiko RF. Steady-state pharmacokinetics of controlled-release oral morphine sulphate in healthy subjects. *Clin Pharmacokinet* 1986; 11:505–510.